

REMARKS

Claims 13-16 presently appear in this case. No claims have been allowed. The official action of September 25, 2001, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for inhibiting the cytotoxic effect of TNF without blocking TNF binding to the p75 TNF receptor. This is accomplished by bringing to the vicinity of TNF a molecule which includes the antigen binding portion of antibodies which are specific to certain regions of the p75 TNF receptor.

The examiner has noted applicants' election without traverse of claims 12-16 in paper no. 4. Claims 1-11 have now been deleted without prejudice towards the continuation of prosecution thereof in a divisional application.

The examiner states that applicant is invited to verify that the instant claims have written support and enablement under 35 USC 112, first paragraph, to priority U.S. and foreign applications.

Applicant now verifies that the subject matter of the present claims is supported by parent application no. 08/476,862 and grandparent application 08/321,685. The subject matter of the claims is not supported in U.S. applications 07/930,443 and 07/524,263. Furthermore, the

subject matter of these claims is believed to be supported by Israeli application 107,267 filed October 12, 1993, but not by the three Israeli priority applications 90,339, 91,229, and 94,039 previously claimed. Accordingly, page 1 of the present specification has now been amended to refer only to those applications for which there is support for the present claims, and a new application data sheet is attached hereto clarifying which prior U.S. applications and which prior Israel priority applications applicant now claims benefit under 35 USC 120 and 119. EP 398,327 published November 22, 1990, which corresponds to the subject matter of application 07/524,263, is of record in this case. It should be noted that while monoclonal antibody 67 is disclosed therein, there is no suggestion therein that this antibody can be used in a method for inhibiting the cytotoxic effect of TNF without blocking TNF binding to the p75 TNF receptor. Indeed, it would be expected by anyone reading this reference that all of the antibodies disclosed therein would block TNF binding to the p75 TNF receptor. It was unexpected that an antibody which did not block binding of TNF to the TNF receptor could still inhibit the cytotoxic effect of TNF.

The examiner has required that applicant amend the first line of the specification to update the status of application 08/476,862. Applicant has now updated this

portion of the specification to update the status in accordance with the examiner's request and in the manner discussed above.

It is noted that the examiner has acknowledged receipt of formal drawings which comply with 37 C.F.R. §1.84. The examiner has reminded applicant to change the brief description of the drawing to refer to these changes. The brief description of the drawings has now been amended in order to comply with this requirement.

The examiner has required applicant to review the application and that all spelling, TRADEMARKS and like errors be corrected. The examiner states that trademarks should be capitalized wherever they appear and be accompanied by generic terminology.

The specification has now been reviewed and all words which have been identified as trademarks have been treated as suggested by the examiner. Documentation supporting the generic terminology added for AFFIGEL 10 and BLUESCRIPT is attached hereto. The generic terminology for PROMEGA TNT is self-evident from context. No spelling errors were noted. If the examiner notes any spelling errors or any other trademarks which should be so identified, then it is respectfully requested that the examiner bring this to

applicant's attention so that appropriate corrections can be made.

Claims 12-16 have been rejected under 35 USC 112, first paragraph, as lacking adequate written description. The examiner states that the specification does not provide adequate written description of the claimed invention for "the natural ligand receptor of the TNF/NGF receptor family", "TBP-II", and "p75 TNF receptor" because the relevant identifying characteristics such as structure or other physical and/or chemical characteristics of said molecules are not set forth in the specification as filed, commensurate in scope with the claimed invention. This rejection is respectfully traversed.

The present claims have now been amended in order to obviate this rejection. Claim 12 has now been deleted, and claim 13 rewritten in independent form. Furthermore, the sequence of the p75 TNF receptor recited therein has been inserted in the claim and the term "TBP-II" is no longer used (although note that this term is defined in Figure 2).

Claim 13 is commensurate in scope with the antibody claim which was allowed in the parent application (now U.S. patent 6,262,239) with the exception that the proviso disclaiming the monoclonal antibody from clone 67 does not appear in present claim 13. This proviso was necessary in the parent case as the antibody of clone 67 as disclosed, for

example, in EP 398 327, would otherwise have anticipated the antibody claim in the parent case. However, such disclosure of the antibody without the disclosure of the unique and unexpected properties thereof, does not make obvious the present method of use claim. Reconsideration and withdrawal of this written description rejection is therefore respectfully urged.

Claims 12-16 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for "TNF-R as set forth in SEQ ID NO:2", "amino acid residues of 163-201 as the 67 group specificity", and "Thr-181 - Asp 235 of SEQ ID NO:2 as the stalk region specificity" does not reasonably provide enablement for any "natural ligand receptor of the TNF/NGF receptor family", "TBP-II", and "p75 TNF receptor", as well as any "67 group specificity" or "stalk region specificity" or "function of the natural ligand receptor of the TNF/NGF receptor family." The examiner states that the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with these claims. This rejection is respectfully traversed.

As discussed above, the claims have now been amended so as only to recite those features which the examiner concedes to be enabled. Accordingly, this rejection has now

been obviated. Reconsideration and withdrawal of this rejection are respectfully urged.

With respect to claim 16, the examiner states that it is apparent that the antibody 67 is required to practice the claimed invention. The examiner states that amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. However, the examiner states that given the disclosure, the conditions for the deposit of biological materials have been satisfied.

It is not understood whether the examiner is requiring anything by these comments. In any event, the examiner's attention is invited to page 30, paragraph 0076, of the present specification, in which the name and address of the depository and the date of deposit are already specified. As the examiner notes, the conditions for the deposit of the biological materials were fully satisfied during the prosecution of the parent case. Attached hereto is a declaration of biological material deposit, signed by the depositor/assignee, and two supporting declarations under 37 C.F.R. §1.804. These are accurate copies of the documents filed in parent application 08/476,862 on October 12, 2000. These documents satisfy all requirements with respect to the deposit of CNCM I-1368.

Reconsideration and withdrawal of any requirement that may be present in paragraph 9 of the official action is therefore respectfully urged.

Claims 12-16 have been rejected under 35 USC 112, second paragraph, as being indefinite in the recitation of "inhibiting the function of the natural ligand receptor of the TNF/NGF receptor of the TNF/NGF receptor family ..." because the nature and metes and bounds of "functions", "vicinity", "group" and "region" are ill-defined and ambiguous. With respect to "vicinity" the examiner states that it is not clear whether this term refers to direct or indirect binding by the claimed antibody specificities, and that if the claims are encompassing indirect binding, then the term "vicinity" is a relative term which renders the claims indefinite. The examiner states that the term is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. This rejection is respectfully traversed.

The present claims have now been amended so as to obviate this rejection with respect to all terms except for "vicinity". The examiner's objection to the term "vicinity" may be based on an error which had appeared in claim 12. It was intended to specify that the peptide or antibody be

brought into the vicinity of the receptor rather than the TNF. It is clear from the language of the claim and the supporting specification that the antibody binds the receptor directly. Thus, the term "vicinity" is no longer a relative term and those of ordinary skill in the art would understand that the term "vicinity" means that the antibodies are brought close enough to the receptor that they can bind the receptor. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 13-16 have been rejected as being indefinite in the recitation of "said extracellular domain" which does not have antecedent basis.

The term "said extracellular domain" no longer appears in the claims, thus obviating this part of the rejection. It is noted, however, that an error occurred in claim 13, last line, where it referred to "residues 202-257 of SEQ ID NO:2". It is clear from page 4, line 23, of the specification that the domain should have been residues 201-257 of SEQ ID NO:2. This correction has now been made.

The examiner states that claims 13-16 are indefinite in that the recitation of "said antibody is a peptide or antibody" is ambiguous and confusing.

Claim 13 has now been amended so as to eliminate the term which the examiner considers to be ambiguous or

confusing. It is believed that the new language obviates this rejection.

The examiner states that applicant should specifically point out the support for any amendments made to the disclosure.

All amendments to the disclosure have already been discussed hereinabove including an indication of why the additions are not new matter.

Accordingly, reconsideration and withdrawal of all of the 35 USC 112, second paragraph, rejections are respectfully urged.

It is noted that the examiner considers that the instant methods as they read on employing antibodies directed toward amino acid residues 163-201 and Thr-181 to Asp-235 of SEQ ID NO:2 as the stalk region specificity appear to be free of the prior art.

All declarations filed in the parent case, have now been made of record in this case and discussed above.

It is submitted that all the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

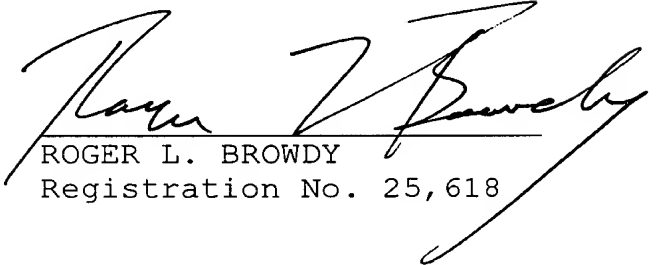
Attached hereto is a marked-up version of the changes made to the specification and claims by the current

amendment. The attached page is captioned "Version with
markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Paragraph 1 beginning at line 3 of page 1 has been amended as follows:

The present application is a division of U.S. application no. 08/476,862, filed June 7, 1995, now U.S. patent 6,262,239, which is a continuation-in-part of U.S. application no. ~~07/930,443, filed on August 19, 1992, and a continuation-in-part of U.S. application no. 08/321,685, filed October 12, 1994, now abandoned, the entire contents of which is hereby incorporated herein by reference.~~—~~The entire contents of both of said applications are hereby incorporated herein by reference. Application no. 07/930,443, filed on August 19, 1992, is a continuation of application no. 07/524,263, filed May 16, 1990, now abandoned.~~

Paragraph 45 beginning at line 22 of page 14 has been amended as follows:

Figures 2A-C shows the nucleotide (SEQ ID NO:1) and deduced amino acid (SEQ ID NO:2) sequences of the p75 receptor. TBP-II and transmembranal domains are boxed and shaded. The region recognized by the group 67 antibodies is underlined, and the region recognized by the anti-stalk antibodies is underlined by a broken line.

Paragraph 71 beginning at line 2 of page 27 has been amended as follows:

In order to compare the function of the 67 group antibodies, not only to antibodies which bind to the receptor at the 67 epitope region, but also to antibodies that bind to the receptor downstream to that epitope region, we immunized rabbits with a chimeric construct corresponding to the region extending downstream to the 32 epitope (amino acids 181 to 235; the "stalk" region), linked to MBP. The rabbits developed antibodies which bound to the chimera with which they were immunized as well as to the intact p55 TNF receptor. These antibodies were affinity purified by binding to the chimeric protein, linked to an Affigel-AFFIGEL 10 column (N-hydroxysuccinimide ester of a derivatized cross-linked agarose gel bead support, available from Bio-Rad Laboratories), and tested for effect on TNF function and binding. (The affinity purified antibody preparation was termed "318"). The mapping of epitope 67 was carried out by examining the ability of antibodies number 67 and 13 (an antibody that binds to the upper part of the extracellular domain of the p75 TNF-R) as well as antiserum 318, to immunoprecipitate the following methionine-labeled soluble p75 TNF-R mutants: WT- a receptor extending from amino acid 22 to amino acid 234, D4D- a

receptor like WT, from which the 4th cysteine-rich domain has been deleted (amino acids 141 to 180). The receptors were produced by *in vitro* transcription of cDNAs encoding them (from the ~~Bluescript~~ BLUESCRIPT vector (a phagemid vector derived from pUC19, available from Stratagene), using the T7 promoter) followed by *in vitro* translation using the ~~Promega~~ TnT-PROMEGA TNT kit (an *in vitro* translation kit available from Promega). The immunoprecipitated proteins were analyzed by SDS PAGE, followed by autoradiography. (A)

Immunoprecipitation of WT. All antibodies were effective.

(B) Immunoprecipitation of D4D. Only antibodies 13 and 318 were effective. The findings indicate that epitope 67 is located at the upper part of the 4th cysteine rich domain, within about amino acids 141 to 180.

In the claims:

Claims 1-12 have been canceled.

Claims 13 and 15 have been amended as follows:

13 (Amended). A method of inhibiting in accordance ~~with claim 12, wherein said extracellular domain of said~~ ~~receptor is TBP-II and said antibody is a peptide or antibody~~ ~~which inhibits the cytotoxic effect of TNF but does not block~~ without blocking TNF binding to the p75 TNF receptor (residues 27-210 of SEQ ID NO:2), comprising bringing to the vicinity of

the p75 TNF receptor a ~~said~~ peptide or antibody comprising the antigen binding portion of an antibody which binds to the fourth cysteine rich domain of the p75 TNF receptor, which domain consists of the sequence of amino acid residues 163 to 201 of SEQ ID NO:2, or to the region between said fourth cysteine rich domain of the p75 TNF receptor and the cell membrane, which region consists of the sequence of amino acid residues 2021-257 of SEQ ID NO:2.

15 (Amended). A method in accordance with claim 13, wherein said peptide or antibody comprises the antigen binding portion of an antibody which binds to the ~~p75 TNF receptor in a region which comprises Thr-179 to the end of the extracellular domain thereof, which region consists of the~~ sequence of amino acid residues 201-257 of SEQ ID NO:2.